REMARKS

The present application is a Continued Prosecution Application of Application Serial No. 09/355,664 filed October 8, 1999. The Official Action dated May 2, 2002 issued in the parent application has been carefully considered. It is believed that the changes presented herewith, taken with the following remarks, are sufficient to place the application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, claims 7 and 8 are amended to clarify that the amino acid residues which are removed are terminal amino acid residues in accordance with the teachings of the specification, for example at page 2, lines 28-30 and page 6, lines 17-28. Claim 9 is amended to omit its dependency on claim 6, and therefore its indirect dependency on claims 5, 4 and 1. Support for claim 9 as presented may be found in the specification at page 2, lines 28-30. A Version With Markings Showing Changes Made is attached. Claims 42 and 43 are added, support for which may be found in original claims 1 and 4-6, and throughout the specification. It is believed that these changes do not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

In the Official Action, claims 1, 2 and 4-9 were rejected under 35 U.S.C. §112, first paragraph. The Examiner asserted that while the specification is enabling for the modified human growth hormone receptor (hGHR) consisting of residues 32-237 of the native molecule of hGHR, capable of being crystallized without being complexed to a ligand molecule, the specification is not enabling for a modified extracellular domain of a cytokine receptor protein as recited in these claims. The Examiner asserts that the specification fails to provide any guidance on how to identify a "molecular segment which contributes to a disordered structure" of a cytokine receptor protein and that the single working example of a modified hGHR consisting of residues 32-237 of the native hGHR molecule does not enable a skilled practitioner to practice the full scope of the claimed invention with any cytokine receptor proteins.

However, Applicants submit that the modified proteins defined by claims 1, 2 and 4-9 are fully enabled by the present specification in accordance with the requirements of 35 U.S.C. §112, first paragraph. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

Contrary to the Examiner's assertions, Applicants submit that it is well within the ability of one of ordinary skill in the art, and in fact easy, to determine parts of a cytokine receptor protein which contribute to a disordered structure for deletion according to the present invention. The Examiner's attention is directed to the specification at page 4, lines 16-31 wherein steps for this determination are described. Specifically, the extracellular portions of cytokine receptor proteins have known primary amino acid sequences and are studied when bound to a ligand, for example the native ligand, by conventional crystallographic methods, for example crystallization and X-ray structure determination or nuclear magnetic resonance (NMR) techniques, to determine binding portions. Specifically, one of ordinary skill in the art knows that the basic structural unit of proteins is amino acids and amino acid units are very often arranged so as to form periodic, secondary structures such as the alpha helix, the beta-plated sheet, and the triple helix. Regions or parts of the proteins with these highly ordered structures connect to one another in a larger three-dimensional structure that forms a functional part, i.e., binding or enzymatic activity, of the protein. The connecting parts of these regions are generally small stretches of unordered amino acids with a high degree of motional freedom. These portions are obviously not possible to remove from the soluble binding receptor protein while maintaining binding activity. However, other parts of the binding protein with such disordered structures that do not contribute to the formation of the binding function can be identified through the aforementioned X-ray and NMR techniques and can be removed.

In the example set forth in the present specification, a disordered portion on each of the N-terminal and C-terminal portions of the soluble receptor was identified through X-ray

studies. At page 6, lines 11-28, the specification specifically discloses that such techniques were employed to form truncated $hGHR_{32-237}$ and $hGHR_{32-234}$, both of which crystallized in the absence of a ligand molecule, in contrast to the native extracellular soluble receptor $hGHR_{1-237}$ which did not crystallize in the absence of a ligand molecule.

Thus, the present specification at page 4 provides a broad description of the methods for determining a molecular segment which contributes to a disordered structure and at page 6 a specific example employing hGHR.

Moreover, hGHR is well recognized in the art as representative of cytokine receptor proteins. In this regard, the Examiner's attention is directed to the DeVos et al publication, "Human Growth Hormone and Extracellular Domain of its Receptor: Crystal Structure of the Complex," *Science*, 255:306-312 (1992) cited in Applicants' Information Disclosure Statement. DeVos et al teach that the growth hormone receptor, along with endocrine hormone receptors, other cytokine receptors, granulocyte and granulocyte-macrophage colony-stimulating factors, and erythropoietin are grouped together in the hematopoietic superfamily (page 306, left column) and that human growth hormone binding protein can serve as a good model for related receptors of the superfamily (page 312, left column). Similarly, the Muller et al publication, "The Crystal Structure of the Extracellular Domain of Human Tissue Factor Refined to 1.7 Å Resolution," *J. Mol. Biol.*, 256:144-159 (1996), cited by the Examiner, recognizes hGHR as providing experimentally derived structural information for class I cytokine receptor superfamily structures (page 145, left column). The Examiner's attention is additionally directed to the Kaczmarski et al abstract of "The Cytokine Receptor Superfamily," *Blood Rev.*, 5(3):193-203 (1991) which discloses that various cytokine receptors have structural homology that is shared by receptors for growth hormone and prolactin, which together make up the cytokine receptor superfamily and that detailed study of individual receptors holds clues to the regulation of receptor expression, ligand-receptor interactions and mechanisms involved in signal transduction.

These publications therefore demonstrate that growth hormone receptor protein is recognized in the art as representative of the cytokine receptor protein superfamily. Thus, the specific example set forth in the present specification is representative to one of ordinary skill in the art of modified cytokine receptor proteins generally as set forth in claim 1.

Accordingly, the broad and specific teachings in the present application enable one of ordinary skill in the art to identify a molecular segment which contributes to a disordered structure for deletion in cytokine receptor proteins in accordance with the claimed invention. Thus, claims 1, 2 and 4-9 are enabled by the present specification in accordance with the requirements of 35 U.S.C. §112, first paragraph. It is therefore submitted that the rejection has been overcome. Reconsideration is respectfully requested.

Claims 1-10 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner asserted that in claim 1, the meets and bounds of the phrase "a molecule segment which contributes to a disordered structure" are not clear. The Examiner asserted that claims 4 and 5 are indefinite because the extent of truncation is not defined, and in claims 7 and 8, the Examiner asserted that precise information about truncation is critical for clearness of the claim.

However, Applicants submit that claims 1, 2 and 4-10 are definite in accordance with the requirements of 35 U.S.C. §112, second paragraph. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More particularly, regarding the phrase "at least one molecule segment which contributes to a disordered structure", it is believed that the remarks set forth above with respect to the rejection under 35 U.S.C. §112, first paragraph, demonstrate that the phrase is not indefinite to one of ordinary skill in the art. That is, as set forth above, such segments can be determined by X-ray analysis, NMR or the like and are those portions of the binding protein with disordered structure that does not contribute to the binding function. Thus, claims 4 and 5 are also clear to one of ordinary skill in the art as truncation refers to removal

of a terminal end segment which contributes to such a disordered structure. With respect to claims 7 and 8, these claims have been amended to further clarify that the amino acid residues which are removed are terminal amino acid residues. Thus, claims 1, 4, 5, 7 and 8, and the claims dependent thereon, are definite to one of ordinary skill in the art, in accordance with the requirements of 35 U.S.C. §112, second paragraph. It is therefore submitted that the rejection has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the Examiner's rejections under 35 U.S.C. §112, first and second paragraphs, and places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Respectfully submitted,

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VERSION WITH MARKINGS SHOWING CHANGES MADE

Claims 7-9 are amended as follows:

7. (Amended) A modified human growth hormone receptor (hGHR) according to claim 6 having 31 or 32 terminal amino acid residues removed in its N-terminal end.

8. (Twice Amended) A modified human growth hormone receptor (hGHR) according to claim 6 having 3 or 4 terminal amino acid resides removed in its C-terminal end.

9. (Third Amendment) A modified growth hormone receptor (hGHR) [according to claim 6] consisting of residues 32-237, 32-234 or 34-233 of the native hGHR molecule.